Introduction: Solving the Clinical Problem of Vancomycin Resistance

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Vancomycin was isolated by scientists at Eli Lilly and Company (Lilly) in the mid-1950s from a soil sample obtained in the interior jungle of Borneo. The organism producing vancomycin was identified as a Streptomyces species (now known as Streptomyces orientalis, subsequently renamed Amycolatopsis orientalis) [1]. Because of the rapid emergence of penicillin resistance in staphylococci, the drug, which has an outstanding spectrum of activity against Gram-positive cocci, including staphylococci, streptococci and enterococci, was rapidly approved by the United States Food and Drug Administration. Nonetheless, it was not widely used by clinicians, because it was perceived to have significant ototoxicity and nephrotoxicity. As it turns out, much of this toxicity may have been due to impurities in the original preparations (dubbed “Mississippi mud” because of the brown-black color of the powder) [2].

Methicillin and the other antistaphylococcal penicillins were developed concomitantly and were much more widely used by clinicians, who considered them safer and at least equally efficacious drugs for staphylococcal infections.

With the emergence of methicillin resistance in staphylococci, however, vancomycin use began to increase steadily. Interestingly, for the first 35 years after its discovery, the development of resistance among previously susceptible organisms was virtually unknown. However, the emergence of vancomycin resistance in enterococci in the mid-1980s served as a wake-up call, and antibiotic chemists at Lilly began efforts to discover chemical modifications of the basic vancomycin nucleus that would confer activity against vancomycin-resistant organisms [3].

They synthesized numerous derivatives of chloroeremomycin, a close analog of vancomycin, and discovered that the addition of side chains to the vancomycin sugar on the molecule resulted in compounds with activity against vancomycin-resistant enterococci (VRE). A derivative with a chlorobiphenylmethyl group attached to the vancosamine terminal monosaccharide of the disaccharide moiety (oritavancin) showed greatest activity. Originally, the basis for this activity was somewhat puzzling because the modifications were made at a position on the molecule far removed from the putative binding site of vancomycin for D-ala-D-alanine, which enables the antibiotic to inhibit cell wall synthesis in Gram-positive bacteria. A number of theories, including dimerization, which allowed the molecule to bind more tightly to the outer cell envelope of Gram-positive bacteria, were put forth, but none provided a definitive explanation for the activity of oritavancin against VRE [4].

Subsequently, Ge et al were able to demonstrate that a portion of the modified chloroeremomycin molecule containing the vancosamine terminal monosaccharide with a chlorobiphenylmethyl side chain actually had activity enabling it to inhibit the second step in Gram-positive cell wall synthesis [5]. Later work has demonstrated that oritavancin inhibits transpeptidation in VRE by interfering with the ability of D-aspartate to form a cross-link with the penultimate D-alanine in the growing cell wall [6]. As it turns out, oritavancin, the compound synthesized by Lilly with the greatest activity against Gram-positive organisms, is now known
to have yet a third mechanism of action: it interacts with and damages the cell membrane as well, a property shared with other new glycopeptides, including telavancin [7, 8]. The fact that oritavancin has multiple mechanisms of action means that, theoretically at least, it should be less likely to select resistant organisms when introduced into widespread clinical use. Unlike teicoplanin, telavancin, and dalbavancin, which have activity against VRE containing the vanB operon because they do not induce expression of this operon but lack activity against constitutively expressed vanA, oritavancin is active against organisms containing all of the commonly found vancomycin operons, including vanA, vanB, vanC, and vanD.

Although roughly a dozen strains of Staphylococcus aureus containing the vanA operon have been discovered to date, this is not a major mechanism of resistance to vancomycin in staphylococci. Instead, a complex set of genetic alterations has led to strains with intermediate levels of resistance, known as vancomycin-intermediate S. aureus (VISA) (including heteroresistant VISA [hVISA]) or glycopeptide-intermediate S. aureus (GISA), which have been increasingly associated with therapeutic failure of vancomycin [9]. Oritavancin also has activity against these strains, although clinical evidence supporting its use in this setting remains to be defined.

The clinical development of oritavancin from its discovery by Lilly >2 decades ago to the present has occurred at a snail’s pace. During the time that oritavancin was being subjected to initial clinical trials at Lilly, the management at Lilly decided to markedly curtail their antibiotic discovery and development activities. The drug was subsequently licensed to InterMune, which carried out a number of phase 3 trials but decided not to continue development of the drug. Oritavancin was then licensed to Targanta (now part of The Medicines Company), which is carrying out the definitive phase 3 trials necessary for its approval.

The lag phase in development of oritavancin bracketed another important development in the United States (and in the rest of the world)—namely, the emergence of community-associated, methicillin-resistant S. aureus [10]. These organisms have now supplanted methicillin-susceptible S. aureus as the most common cause of acute bacterial skin and soft-tissue infections in the United States. Many of these infections, although serious, can be treated on an outpatient basis. As a result, there is a growing need for better oral antistaphylococcal drugs (which oritavancin is not) or for parenteral agents with long half-lives that can be given infrequently to treat such infections. In this latter regard, the flexibility in dosing of oritavancin, which allows it to be given only once or twice to complete a course of therapy for most non–life-threatening skin and skin structure infections, is a major potential advantage. Although a parenteral agent with obvious potential in the inpatient setting, oritavancin could also be effectively used to treat outpatient infections without the need for daily (or even more frequent) intravenous infusions.

The rationale for the single-dose regimen in the current phase 3 trials is found in a recently completed phase 2 trial and animal model studies carried out by Craig and his colleagues and reported in this supplement [11]. The remainder of the papers in this symposium define the activity, clinical utility, and safety of oritavancin and provide the basis for our understanding of the potential place of this new drug in our therapeutic armamentarium, at a time when there is a clearly defined need for new effective antimicrobial agents.

References